

# Electrophysiological properties of phentolamine in man

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*The effects of phentolamine, 0.3 mg/min given intravenously for 15 minutes, on His bundle electrograms were studied in 11 patients with heart disease. Recordings were made at varied heart rates, using atrial pacing. Phentolamine significantly reduced the AH interval in every patient but it had no effect on the HV interval. Functional and effective refractory periods were measured with the use of the atrial extrastimulus technique. The effective refractory period of the atrium and atrioventricular node as well as the functional refractory period of the atrioventricular node all significantly decreased after phentolamine infusion. This improvement in conduction is probably mediated by a release of catecholamines.*

In his experimental work on dogs, Leimdorfer (1952) showed that the intravenous administration of phentolamine prevented the induction of arrhythmias by nicotine sulphate and adrenaline, and converted methacholine-induced atrial flutter to normal sinus rhythm. He further showed that phentolamine administration prevented the appearance of pronounced bradycardia during electrical stimulation of the vagus nerve. Vargaftig and Coignet (1969) showed that the appearance of aconitine-induced arrhythmias in rats was delayed by phentolamine, and, in addition, ventricular fibrillation caused by chloroform inhalation in mice was blocked by phentolamine.

The antiarrhythmic effect of phentolamine was investigated in 10 normal dogs acutely digitalised with ouabain (Ettinger *et al.*, 1969). Phentolamine was infused for an average of 10 minutes at 0.3 mg/min. Ventricular arrhythmias were abolished in 7 of 8 dogs and the rate was increased in 1 dog with sinus bradycardia. It was subsequently reported that the intravenous administration of phentolamine could successfully suppress digitalis or non-digitalis induced ventricular premature beats in man (Gould *et al.*, 1969). Similarly, phentolamine infused at a rate of 0.3 mg/min for 15 minutes decreased or abolished supraventricular premature beats in 22 of 30 patients (Gould *et al.*, 1972). The oral administration of phentolamine was also effective in suppressing ventricular premature beats in cardiac patients without an acute myocardial infarction

(Gould *et al.*, 1971). Recently the effectiveness of phentolamine therapy for the prevention of cardiac arrhythmias was determined in a double blind study of 39 patients with uncomplicated acute myocardial infarction (Gould *et al.*, 1975). Phentolamine, 50 mg, or placebo was administered orally 4 times a day for 5 days. Phentolamine afforded a highly significant protection from ventricular premature beats and supraventricular premature beats.

The effect of phentolamine on atrioventricular conduction has been studied in patients using the His bundle electrogram technique. A shortening of the AH interval, which signifies an improvement in atrioventricular conduction, was found by two groups of workers (Khan *et al.*, 1972; Gould *et al.*, 1974). However, no study has been reported of its effect on the refractory periods of the atrium and atrioventricular node as determined by the extrastimulus method.

The present study, involving 11 human subjects, was undertaken to determine what effects intravenously administered phentolamine has on refractoriness of the atrium and atrioventricular node at paced cycle lengths. Measurements were also made of the atrioventricular nodal and His-Purkinje conduction time over a range of paced atrial beats.

## Subjects and methods

The study group consisted of 11 patients with heart disease. The clinical features of the group are

Table 1 *Clinical data*

Case No.	Age (y)	Sex	Diagnosis	Electrocardiographic findings
1	19	M	Sick sinus syndrome	Sinus bradycardia
2	65	M	Coronary heart disease	Complete right bundle-branch block and old inferior wall myocardial infarction
3	62	M	Syncope—aetiology unknown	Complete right bundle-branch block
4	76	F	Episodes of supra-ventricular tachycardias	Sinus rhythm with non-specific ST-T wave changes
5	54	F	Episodes of supra-ventricular tachycardias	Normal sinus rhythm with non-specific ST-T wave changes
6	51	M	Coronary heart disease	Normal sinus rhythm with non-specific ST-T wave changes
7	62	F	Episodes of supra-ventricular tachycardias	Complete right bundle-branch block
8	80	F	Sick sinus syndrome	Sinus bradycardia
9	60	F	Coronary heart disease	Recent inferior wall myocardial infarction—transient complete heart block
10	58	M	Syncope—aetiology unknown	Complete left bundle-branch block
11	79	F	Sick sinus syndrome	Sinus bradycardia

summarised in Table 1. All patients were informed of the nature of the study and gave informed consent. They were studied in the supine position in a postabsorptive, nonsedated state.

Under local anaesthesia, a quadripolar electrode catheter was introduced percutaneously into the right antecubital vein and fluoroscopically positioned against the lateral wall of the high right atrium near its junction with the superior vena cava. The distal pair of electrodes was used to stimulate the atrium while the proximal pair was used to record a high right atrial electrogram. In addition, a bipolar pacing catheter was introduced percutaneously into the right femoral vein and fluoroscopically positioned at the tricuspid valve. The position was adjusted to obtain optimal recordings of the bundle of His electrogram. The proximal terminals of the catheter were attached to an electrocardiographic amplifier, and the bipolar His electrogram was recorded at a frequency setting of 40 to 500 cycles/s on a DR-12 Electronics for Medicine recorder at paper speeds of 100 mm/s. Simultaneous electrocardiographic leads I, II, and III were recorded.

Conduction studies were carried out during sinus rhythm and at various paced atrial rates up to a maximum of 190 beats/minute. Atrial stimulation was performed using a programmed digital stimulator that delivered impulses of 1.5 ms duration at approximately twice diastolic threshold.

The refractory periods of the atrium, atrioventricular node, and His-Purkinje system were determined by the extrastimulus method (Wit *et al.*, 1970). A cycle length approximately 20 per cent faster than the sinus rate was used so that refractory periods could be measured at identical cycle lengths before and after administration of phenolamine. The following intervals were measured in milliseconds.

#### (1) PA INTERVAL

The interval from the onset of the P wave during normal sinus conduction recorded on the standard electrocardiographic lead to the first rapid deflection of the A wave on the bipolar electrogram. The PA time represents intra-atrial conduction time. The normal value is  $27 \pm 18$  ms (Rosen, 1972). During atrial pacing the PA time is measured from the pacing impulse to A.

#### (2) AH INTERVAL

The interval from the first rapid deflection of the A wave to the first rapid deflection of the bundle of His electrogram. The AH time represents conduction time through the AV node. The normal value is  $92 \pm 38$  ms (Rosen, 1972).

#### (3) HV INTERVAL

The interval from the first rapid bundle of His deflection to the onset of the QRS deflection in the electrocardiogram. The HV interval approximates conduction time in the specialised tissues of the His-Purkinje system. The normal value is  $43 \pm 12$  ms (Rosen, 1972).

For the assessment of each of these intervals, measurements were made from 10 beats before and after the administration of phenolamine, and the mean values were used for comparison. In addition, the recovery time of the sinus node pacemaker, after sudden cessation of the highest pacing rate obtained, was observed before and after the drug.

The following definitions were used in regard to refractory periods:  $A_1$ ,  $H_1$ , and  $V_1$  were the atrial, His bundle, and ventricular electrograms of driven beats ( $S_1$ ).  $A_2$ ,  $H_2$ , and  $V_2$  were the atrial, His bundle, and ventricular electrograms in response to the extrastimulus ( $S_2$ ). The atrial effective refractory period was the longest  $S_1$ - $S_2$  interval at which  $S_2$  did not result in atrial depolarisation. The atrioventricular nodal effective refractory period was the longest  $A_1$ - $A_2$  interval at which  $A_2$  failed to conduct to the bundle of His. The atrioventricular nodal functional refractory period was the shortest interval between  $H_1$ - $H_2$ , both of which were propagated from the atrium.

**Table 2** Summary of atrioventricular and intraventricular conduction (in ms) in 11 patients before and after phentolamine administration

	No. of patients	State	Mean $\pm$ SEM	P value
Sinus rate (beats/min)	11	C	69 $\pm$ 6	< 0.01
		P	74 $\pm$ 6	
Blood pressure (mmHg)	11	C	145/83 $\pm$ 8/4	< 0.01
		P	130/70 $\pm$ 6/3	
PA interval	11	C	29 $\pm$ 3	NS
		P	28 $\pm$ 3	
AH interval	11	C	93 $\pm$ 6	< 0.05
		P	89 $\pm$ 6	
HV interval	11	C	49 $\pm$ 4	NS
		P	49 $\pm$ 4	
AH interval (at HR 100/min)	9	C	141 $\pm$ 13	< 0.01
		P	116 $\pm$ 12	
AH interval (at HR 120/min)	8	C	165 $\pm$ 13	< 0.01
		P	132 $\pm$ 12	
Sinus nodal recovery time	11	C	1060 $\pm$ 76	NS
		P	1021 $\pm$ 78	
Heart rate during Wenckebach periods (beats/min)	11	C	136 $\pm$ 8	< 0.001
		P	147 $\pm$ 8	

HR, heart rate; NS, not significant; C, control; P, phentolamine.

Phentolamine was then infused intravenously at 0.3 mg/min for 15 minutes and the electrophysiological studies were repeated. The blood pressure was also obtained, with a sphygmomanometer, before and after the administration of phentolamine. Statistical analysis of all data was performed using the Student's *t* test for paired data.

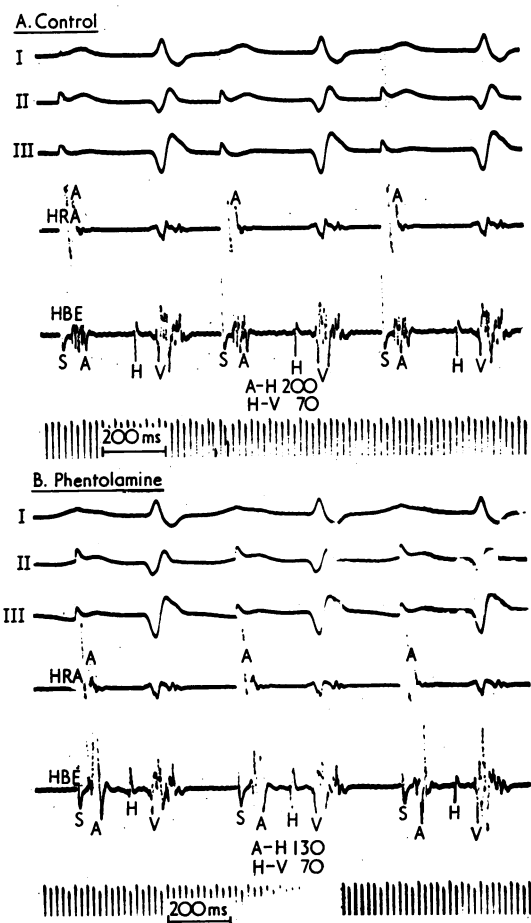
## Results

The effects of phentolamine on the conduction system are presented in Tables 2 and 3.

**Table 3** Effects of phentolamine on refractory periods of atrioventricular conducting system

Case No.	Paced cycle length (ms)	ERP of atrium (ms)		ERP of AV node (ms)		FRP of AV node (ms)	
		Pre	Post	Pre	Post	Pre	Post
1	1000	240	240	540	490	630	550
2	600	270	230	340	330	480	460
3	700	260	250	365	270	520	430
4	700	270	260	390	360	500	480
5	600	230	230	*	—	520	440
6	600	200	200	300	290	420	380
7	600	180	170	*	—	430	420
8	600	380	345	*	—	515	490
9	600	280	270	450	440	550	540
10	450	330	170	*	—	380	320
11	600	340	260	420	320	560	480
Mean $\pm$ SEM		273 $\pm$ 18 Pre	239 $\pm$ 15 Post	401 $\pm$ 30 Pre	358 $\pm$ 31 Post	500 $\pm$ 21 Pre	454 $\pm$ 21 Post
P value		< 0.05		< 0.05		< 0.001	

\*Electrophysiological studies limited because of atrial refractoriness. ERP, effective refractory period; FRP, functional refractory period.



**Fig. 1** His electrogram obtained in case 3 at paced atrial rate of 120 beats/min before (A) and after (B) phentolamine infusion. Each panel is organised as follows: From top to bottom, standard leads I, II, III, high right atrial electrogram (HRA), His bundle electrogram (HBE), and time lines of 20 ms. AH interval and HV interval before phentolamine therapy were 200 and 70 ms, respectively. After administration of phentolamine HV interval was unchanged, while AH interval decreased to 130 ms.

## INTRA-ATRIAL CONDUCTION

The PA interval was measured in all patients. The mean PA interval  $\pm$  standard error of the mean was 29  $\pm$  3 before and 28  $\pm$  3 ms after phentolamine administration (NS). The atrial effective refractory periods could be measured in 11 patients. The mean effective refractory period of the atrium was 273  $\pm$  18 ms before and 239  $\pm$  15 ms after phentolamine administration (*P* < 0.05).

#### ATRIOVENTRICULAR NODAL CONDUCTION

AH intervals could be measured in all patients. The mean AH interval during sinus rhythm was  $93 \pm 6$  ms before and  $89 \pm 6$  ms after administration of phentolamine ( $P < 0.05$ ). With atrial pacing AH intervals at equivalent paced rates (100 to 120/min) were significantly different before and after phentolamine. For example, the mean AH interval at a paced rate of 100/min in 9 patients was  $141 \pm 13$  ms before and  $116 \pm 12$  ms after phentolamine ( $P < 0.01$ ). At a pacing rate of 120/min the AH interval was  $165 \pm 13$  ms before and  $132 \pm 12$  ms after phentolamine ( $P < 0.01$ ) (Fig. 1). The paced rate at which Wenckebach periods proximal to the His bundle occurred was noted in 11 patients. This mean rate was  $136 \pm 8$  beats/min before and  $147 \pm 8$  beats/min after phentolamine ( $P < 0.001$ ). The mean atrioventricular nodal functional refractory period was  $500 \pm 21$  ms before and  $454 \pm 21$  ms after phentolamine ( $P < 0.001$ ). The effective refractory period of the atrioventricular node was  $401 \pm 30$  ms before and  $358 \pm 31$  ms after administration of phentolamine ( $P < 0.05$ ) (Fig. 2).

#### INTRAVENTRICULAR CONDUCTION

The HV intervals were not changed in any patient by the administration of phentolamine.

#### AUTOMATICITY AND RECOVERY PERIODS OF SINUS NODE

The sinus rate increased in all patients. The mean sinus rate was  $69 \pm 6$  beats/min before and  $74 \pm 6$  beats/min after phentolamine ( $P < 0.001$ ). Sinus node recovery times decreased after phentolamine. Mean recovery times before and after phentolamine were  $1060 \pm 76$  ms and  $1021 \pm 78$  ms, respectively (NS).

#### BLOOD PRESSURE

The blood pressure fell in every patient after phentolamine administration. The mean values were respectively  $145/83 \pm 8/4$  mmHg before and  $130/70 \pm 6/3$  mmHg after phentolamine ( $P < 0.01$ ).

#### Discussion

The present study revealed that phentolamine administration produced a significant reduction in the AH interval in the control state as well as at the various atrial pacing rates. In a previous report from this laboratory, phentolamine was found consistently to enhance atrioventricular nodal conduction in man (Gould *et al.*, 1974). In keeping with those findings is the fact that in this study the functional refractory period of the atrioventricular node decreased in all patients. Further, the effective

refractory period of the atrioventricular node also shortened in the 7 patients in whom this interval could be measured. Phentolamine did not affect His Purkinje conduction time (HV interval) during sinus rhythm or over a wide range of paced atrial rates. The PA interval, a measure of conduction from the high to low right atrium, was unaltered after the administration of phentolamine. It is of interest that the effective refractory period of the atrium showed a small but significant decrease after phentolamine administration.

Phentolamine can increase the availability of endogenous catecholamines to the heart. This contention is supported by the work of Dairman *et al.* (1968). They administered phentolamine 5 mg/kg to rats; at the height of receptor blockade, the conversion of a tracer dose of  $^{14}\text{C}$ tyrosine to norepinephrine was increased threefold, with no alteration in specific activity of tyrosine in blood and tissues. From these studies Dairman and his co-workers concluded that receptor blockade led to increased synthesis and release of noradrenaline in the three organs that were measured.

Bagwell *et al.* (1970) administered 5 mg/kg of phentolamine to seven experimental animals and observed an increase in the left ventricular contractile force. If the animals were pretreated with reserpine the inotropic action of phentolamine could be blocked; a subsequent infusion of noradrenaline could then restore the inotropic effect. They concluded that the positive inotropic action of phentolamine is indirect and dependent on the release of noradrenaline.

It has recently been shown that phentolamine has  $\beta$ -adrenergic stimulating properties as well as its  $\alpha$ -adrenergic blocking effects. This  $\beta$ -adrenergic stimulating action is suggested by the observation that the fall in blood pressure and the increase in cardiac rate produced by 5 mg of phentolamine can be significantly blocked by the prior administration of propranolol (Zahir and Gould, 1971). Propranolol can similarly block the inotropic and chronotropic action of phentolamine in dogs (Singh *et al.*, 1970). The release of catecholamines following the administration of phentolamine explains the improvement observed in conduction through the atrioventricular node.

If phentolamine can increase the availability of endogenous catecholamines to the heart, it is possible that the drug acts, at least in part, in a manner different from most other antiarrhythmic agents. Catecholamines are known to cause hyperpolarisation of partially depolarised or 'sick fibres'. The result is restoration of a normal action potential configuration without significant change in phase 4 (Rosen and Gelband, 1971). By this means,

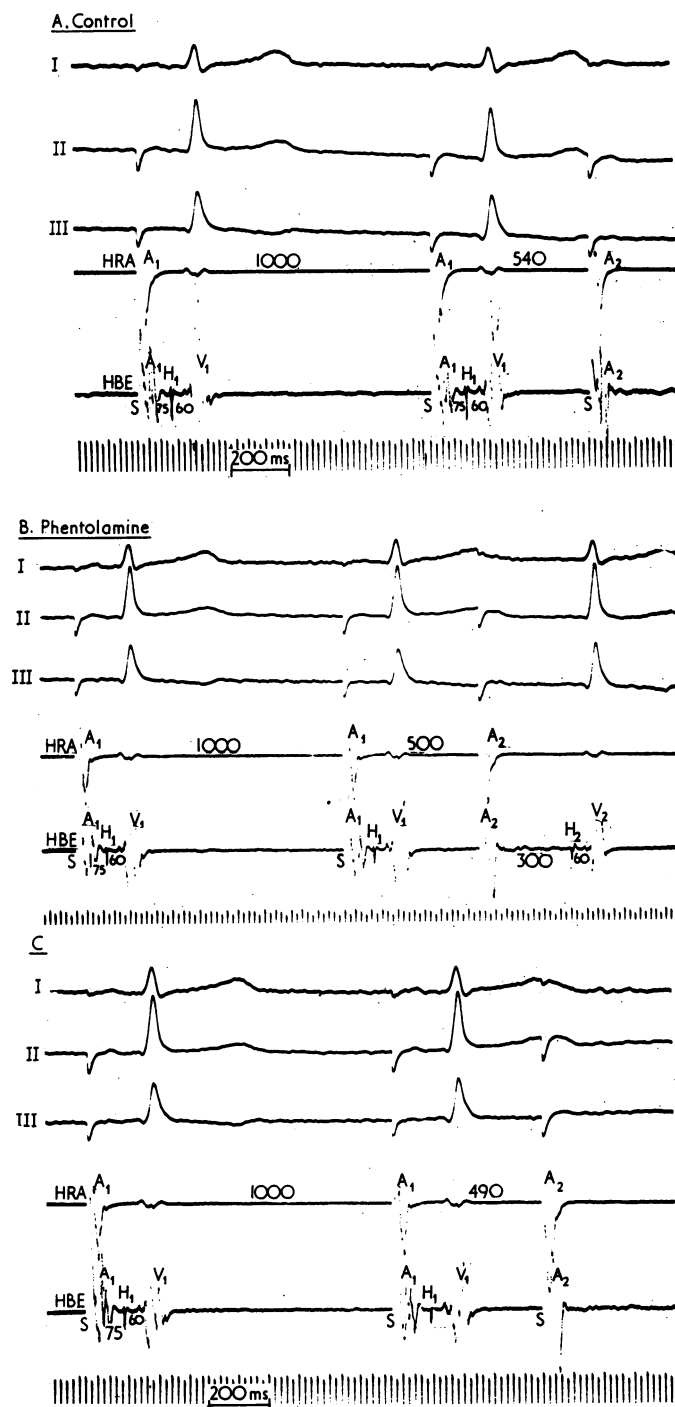


Fig. 2 Effects of phentolamine on the effective refractory period of the atrioventricular node (case 1). Each panel arranged as in Fig. 1. The basic paced atrial cycle length is 1000 ms. In the control panel (A) the effective refractory period of the atrioventricular node is reached at an atrial coupling interval ( $A_1$ - $A_2$ ) of 540 ms. After administration of phentolamine,  $A_2$  continues to conduct to the His-Purkinje system at an  $A_1$ - $A_2$  interval of 500 ms (B). When the  $A_1$ - $A_2$  interval is decreased to 490 ms (C), block of  $A_2$  above the His bundle occurs and the effective refractory period of the atrioventricular node is reached. Thus, phentolamine shortened the effective refractory period of the atrioventricular node by 50 ms.

catecholamines may increase conduction velocity through areas where abnormal conduction is occurring, and hence abolish arrhythmias (Hoffman

and Singer, 1967). It is conceivable that at least part of the antiarrhythmic action noted with phentolamine may be secondary to such a mechanism.

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